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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/699,243	10/27/2000	Isabel D.C. Markl	47675-14	5397

7590 03/05/2002

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EXAMINER
GOLDBERG, JEANINE ANNE

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 03/05/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/699,243	Applicant(s) MARKL ET AL.	
	Examiner Jeanine A Goldberg	Art Unit 1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 December 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of Groups I and II (as rejoined by the examiner) and SEQ ID NO: 34-38 in Paper No. 6 is acknowledged.

Applicant is reminded that prior to allowance, all non-elected subject matter must be cancelled.

Additionally, Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Claim Rejections - 35 USC § 112-Description

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 1-12 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to DNA sequences and methods using DNA sequences having at least 90% identity with SEQ ID NO: 34-38, CpG island sequences associated

with SEQ ID NO: 34-38, CpG island sequences associated with sequence having a nucleotide sequence at least 90% identical to SEQ I DNO: 34-38 and combinations thereof.

The specification describes sequencing 103 "novel" sequences. The specification fails to teach the chromosomal location, the gene, or the cDNA of these DNA sequence fragments.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2b 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed". Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 USC 112 is severable from its ennablement provision. In *The Regents of the University of California v. Eli Lilly* (43 USPQ2b 1398-1412), the court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. At section B(1), the court states that "An adequate written description of a DNA…' required a precise definition, such as by structure, formula, chemical name, or physical properties', not a mere wish or plan for obtaining the claimed chemical invention". In analyzing whether the written description requirement is met for a genus claim, it is first determined

whether a representative number of specifies have been described by their complete structure. In the instant case, Applicant has defined only a fragment of a nucleic acid sequence. Applicant has not disclosed any genomic DNA sequences and particularly has not disclosed any intron sequences or regulatory sequences. Accordingly, Applicants have not adequately disclosed the relevant identifying characteristics of a representative number of species within the claimed genus.

Similar to Example 7 of the Written Description guidelines, the specification teaches a fragment of a cDNA or genomic DNA, but does not provide the full cDNA or genomic DNA.

The specification does not appear to have described any sequences which are 90% identical with SEQ ID NO: 34-38 and have the same asserted function for detecting cancer.

The specification has not provided any description of sequences "associated with SEQ ID NO: 34-38". The specification does not appear to define what "associated" means in a clear and definite way. It is unclear whether "associated" means that the "associated" nucleic acid sequence contains similar nucleotides, is located adjacent to SEQ ID NO: 34-38 on the chromosome, is located on another chromosome, but is involved in the same metabolic pathway or rather associated has a distinct meaning. Therefore, applicants have not described a representative number of these embodiments within the scope of the claim.

Claim Rejections - 35 USC § 112- Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 1-12 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are broadly drawn to a method of diagnosis or prognosis of cancer by performing a methlyation assay to determine a diagnosis.

The specification clearly states that "unfortunately, the mere knowledge of the basic existence of altered methylation of CpG dinucleotides within CpG islands of cancer cells relative to normal cells, or of the fact that in particular instances such methylation changes result in altered gene expression (or chromatin structure or stability), is inadequate to allow for effective diagnostic, prognostic and therapeutic application of this knowledge" (page 2, lines 31-35). The specification continues to state "this is because only a limited number of CpG islands have been characterized, and thus there is insufficient knowledge, as to which particular CpG islands, among many, are actually involved in, or show significant correlation with cancer or the etiology thereof. Moreover, complex methylation patterns, involving a plurality of methylation-altered DNA sequences, including those that may have the sequence compositions to qualify as CpG islands, may exist in particular cancers" (page 3, lines 1-5). Therefore, there is a need in the art to identify and characterize specific methylation altered DNA sequences, and to correlate them with cancer to allow for their diagnostic, prognostic

and therapeutic application (page 3, lines 7-10). The specification teaches the invention provides for 103 DNA sequences having distinct methylation patterns in cancer, as compared to normal tissue (page 5, lines 35-36). These "methylation-altered DNA sequence embodiments correspond to 103 DNA fragments isolated from bladder and prostate cancer patients" (page 6, lines 1-2). Genomic DNA was isolated from tissue of bladder or prostate cancer patients and identified as either hypermethylated or hypomethylated (page 6).

The art clearly illustrates that certain genes, including GSTP1, HIC-1, and p16, are hypermethylated and this is indicative of certain cancers (US Pat. 5552,277; 5,846,712; 5,856,094).

Neither the specification nor the art teach the skilled artisan how to use the invention as broadly as claimed. First, the specification clearly teaches that "unfortunately, the mere knowledge of the basic existence of altered methylation of CpG dinucleotides within CpG islands of cancer cells relative to normal cells, or of the fact that in particular instances such methylation changes result in altered gene expression (or chromatin structure or stability), is inadequate to allow for effective diagnostic, prognostic and therapeutic application of this knowledge" (page 2, lines 31-35). The instant specification does not appear to have performed any more experimentation than the mere determination that a basic existence of altered methylation of CpG dinucleotides within CpG islands of cancer cells relative to normal. Therefore, the specification appears to be indicating that this is inadequate to allow for effective diagnostic, prognostic or therapeutic application of this knowledge. In essence, it

appears as though the specification teaches that the instant invention is not enabled for use in diagnostic, prognostic or therapeutic applications. In order to use this information, the skilled artisan would be required to sample a population of individuals and assess whether each SEQ ID NO: 34-38 is associated differentially expressed in cancer. This experimentation would be trial and error experimentation which would not have predictable results for the reasons provided in the specification, namely "this is because only a limited number of CpG islands have been characterized, and thus there is insufficient knowledge, as to which particular CpG islands, among many, are actually involved in, or show significant correlation with cancer or the etiology thereof. Moreover, complex methylation patterns, involving a plurality of methylation-altered DNA sequences, including those that may have the sequence compositions to qualify as CpG islands, may exist in particular cancers" (page 3, lines 1-5). In the event that detection of cancer, is not enabled, it is unclear how the polynucleotides may be used.

Second, the specification teaches that SEQ ID NO: 34-38 are hypermethylated as opposed to hypomethylated. The claims appear to be directed to determining that the sequence is aberrantly methylated as indication of cancer. However, it is unpredictable that SEQ ID NO: 34-38 are hypomethylated and in the event that SEQ ID NO: 34-38 are hypomethylated that this is indicative of cancer.

Third, the specification teaches SEQ ID NO: 34-38 were found to be hypermethylated in a prostate cancer tissue sample. The indication that one prostate cancer sample indicated a hypermethylation of the region is not indicative that any and all cancers have the same methylation regions. For example, the bladder cancer

samples exemplified in the specification do not appear to have hypermethylation of SEQ ID NO: 34-38. Therefore, it is unpredictable whether hypermethylation of SEQ ID NO: 34-38 is a general marker for all cancers, or whether there is a smaller class of cancers which SEQ ID NO: 34-38 are markers, or finally whether the sequence may only be expressed in prostate cancer.

Finally, the specification has not taught that a predictable correlation exists between nucleic acids which are "associated with SEQ ID NO: 34-38". The specification has not described any associated nucleic acids, therefore, it is unpredictable that "associated DNA sequences" are indicative of cancers absent unpredictable and undue experimentation. The skilled artisan would first be required to determine associated sequences of SEQ ID NO: 34-38 and then assay these unknown sequences to determine whether or not they are hypermethylated or hypomethylated and then whether this aberrant methylation status is associated with cancer.

Therefore, based upon the unpredictability and the undue experimentation which would be required to be performed prior to practicing the full scope of the method, the instant specification has not enabled the instant claims.

Claim Rejections - 35 USC § 112- Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 1-6, 8-9 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claims 1-6 are indefinite over the recitation "derived from" because this language does not particularly set forth whether the sample is unaltered from the tissue sample or whether the sample was originally taken from the tissue sample but are then modified in some way. This rejection may be easily overcome by deleting the word "derived" so that the methylation assay is performed on DNA from the tissue sample.

B) Claims 1-6 are directed to CpG island sequences associated with SEQ ID NO: 34-38. The specification does not appear to define what "associated" means in a clear and definite way. It is unclear whether "associated" means that the "associated" nucleic acid sequence contains similar nucleotides, is located adjacent to SEQ ID NO: 34-38 on the chromosome, is located on another chromosome, but is involved in the same metabolic pathway or rather associated has a distinct meaning. Claim 1 appears to definite CpG island sequences associated with SEQ ID NO: 34-38 as contiguous sequence of genomic DNA that encompasses at least on nucleotide of SEQ ID NO: 34-38. This definition is permissive of a sequence of contiguous nucleotides in a remote location from SEQ ID NO: 34, for example, which contains at least one "A" nucleotide, since SEQ ID NO: 34 contains an "A".

C) Claims 1-6 are directed to "combinations thereof" which does not provide a clear and definite meaning. It is unclear what combinations thereof is intended to modify. It is unclear whether the claim is directed to DNA sequences which are

combinations of SEQ ID NO: 34 and 38 such that they bear little resemblance to either sequence, whether they are combinations of SEQ ID NO: 34 such that the nucleotides are scrambled up in any appropriate manner, or whether the sequences must merely contain ATCG's in any combination. Therefore, the metes and bounds of the claimed invention are unclear.

D) Claim 8 is indefinite because it is unclear what MSP MCA assays are. It appears as though these are two distinct assays outlined on page 13-14 of the specification. Therefore, it appears as though a comma is missing from the claim.

E) Claim 9 is indefinite over the phrase "at least about" because the metes and bounds of the invention are not clear. As the CAFC noted, and affirmed, regarding the district court determination of this phrase in Amgen Inc. v. Chugai Pharmaceutical Co. Ltd. (CA FC) 18 USPQ2d 1016 at page 1031 "the court held the "at least about" claims to be invalid for indefiniteness." Here too, the situation is that there is close prior art, applied as a 102(b) for a lower limit value, and the claim is indefinite with regard to the values encompassed.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5. Claims 7-9 are rejected under 35 U.S.C. 102(b) as being anticipated by Herman et al. (US Pat. 5,786,146, July 28, 1998).

Herman teaches a kit comprising a reagent which modifies unmethylated cytosine and primers for amplification of the CpG –containing nucleic acid (Claim 15)(limitations of Claim 7). Herman teaches a kit comprising SEQ ID NO: 46 which contains "CTAAAAAT" which is embedded within SEQ ID NO: 34 of the instant application. Therefore, this primer, SEQ ID NO: 36 of Herman, would hybridizes to any region of SEQ ID NO: 34-38, namely region of SEQ ID NO: 34, nucleotides 212-219 (8 nucleotides). This primer comprises at least about 12 nucleotides which are at least 90% identical to SEQ ID NO: 34. Alternatively, the primer comprises 10 nucleotides which are 90% identical to SEQ ID NO: 34. The kit contains bisulfite, amplification buffer which is used in COBRA, Ms-SnuPE, MSP, etc. analysis.

Conclusion

6. No claims allowable.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Goldberg whose telephone number is (703) 306-5817. The examiner can normally be reached Monday-Friday 7:00 a.m. to 4:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152. The fax number for this Group is (703) 305- 3014.

Any inquiry of a general nature should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Jeanine Goldberg
February 28, 2002

W. Gary Jones
Supervisory Patent Examiner
Technology Center 1600